10/614481 09/07/2006

Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
****
ENTER PASSWORD:
****
Welcome to DIALOG

Dialog level 05.22.00D

Last logoff: 25nov08 09:01:45
Logon file405 02dec08 14:57:44
*** ANNOUNCEMENTS ***
***

*** Join us for Update 2008! Dialog is holding updates this fall
in several areas and would love for you to join us. Visit
www.dialog.com/events/update to register or enter HELP UPDATES
for more information.

*** "Thomson File Histories" are now available directly through Dialog
in selected patent and trademark files. Combined with the
comprehensive patent and trademark information on Dialog, file
histories give you the most complete view of a patent or trademark
and its history in one place. When searching in one of the patent
and trademark databases, a link to an online order form is displayed
in your search results, saving you time in obtaining the file
histories you need. See HELP FILEHIST for more information about
how to use the link and a list of files that contain the link.

NEW FILE
***File 651, TRADEMARKSCAN(R) - China. See HELP NEWS 651 for details.
RESUMED UPDATING
***File 523, D&B European Financial Records
***

RELOADS COMPLETED
***File 227, TRADEMARKSCAN(R) - Community Trademarks
***

FILES RENAMED
***File 321, PLASPEC now known as Plastic Properties Database
***

FILES REMOVED
***File 601, Early Edition Canada
***

>>>For the latest news about Dialog products, services, content<<<
>>>and events, please visit What's New from Dialog at <<<
>>>http://www.dialog.com/whatsnew/. You can find news about <<<
>>>a specific database by entering HELP NEWS <file number>. <<<
>>>PROFILE is in a suspended state.
>>>Contact Dialog Customer Services to re-activate it.
* * *
SYSTEM HOME
Cost is in DialUnits
Menu System II: D2 version 1.8.0 term=ASCII
*** DIALOG HOMEBASE(SM) Main Menu ***

Information:
1. Announcements (new files, reloads, etc.)
2. Database, Rates, & Command Descriptions
3. Help in Choosing Databases for Your Topic
4. Customer Services (telephone assistance, training, seminars, etc.)
5. Product Descriptions

Connections:
6. DIALOG(R) Document Delivery
7. Data Star(R)

/H = Help /L = Logoff /NOMENU = Command Mode

Enter an option number to view information or to connect to an online
service. Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

02dec08 14:57:44 User217743 Session D745.1

```
            $0.00     0.271 DialUnits FileHomeBase
      $0.00  Estimated cost FileHomeBase
      $0.00  Estimated cost this search
      $0.00  Estimated total session cost    0.271 DialUnits

File 410:Dialog Comm-of-Interest Newsletters 2008 /Mar
      (c) 2008 Dialog

      Set  Items  Description
      ---  -----  -----------
? set hi ;set hi
HILIGHT set on as '*'
HILIGHT set on as '*'
? b 411
       02dec08 14:57:48 User217743 Session D745.2
            $0.00     0.115 DialUnits File410
      $0.00  Estimated cost File410
      $0.02  TELNET
      $0.02  Estimated cost this search
      $0.02  Estimated total session cost    0.386 DialUnits
File 411:DIALINDEX(R)

DIALINDEX(R)
   (c) 2008 Dialog

*** DIALINDEX search results display in an abbreviated ***
*** format unless you enter the SET DETAIL ON command. ***
? set files biochem
   You have 29 files in your file list.
   (To see banners, use SHOW FILES command)
? s IL()6 and crp and cancer

Your SELECT statement is:
   s IL()6 and crp and cancer

          Items   File
          -----   ----
            133     5: Biosis Previews(R)_1926-2008/Nov W4
             17    24: CSA Life Sciences Abstracts_1966-2008/Nov
            176    34: SciSearch(R) Cited Ref Sci_1990-2008/Nov W4
             31    45: EMCare_2008/Nov W4
             15    50: CAB Abstracts_1972-2008/Nov W5
            112    71: ELSEVIER BIOBASE_1994-2008/Nov W8
            206    72: EMBASE_1993-2008/Dec 02
            211    73: EMBASE_1974-2008/Dec 01
              1    76: Environmental Sciences_1966-2008/Nov
              3    98: General Sci Abs_1984-2008/Oct
             84   144: Pascal_1973-2008/Nov W5
            130   154: MEDLINE(R)_1990-2008/Nov 24
            130   155: MEDLINE(R)_1950-2008/Nov 24
             14   156: ToxFile_1965-2008/Nov W2
             28   162: Global Health_1983-2008/Nov W5
              7   172: EMBASE Alert_2008/Nov 27
              7   399: CA SEARCH(R)_1967-2008/UD=14922

   17 files have one or more items; file list includes 29 files.

? b 155
       02dec08 14:59:03 User217743 Session D745.3
            $9.29     3.161 DialUnits File411
      $9.29  Estimated cost File411
      $0.53  TELNET
      $9.82  Estimated cost this search
      $9.84  Estimated total session cost    3.546 DialUnits

File 155:MEDLINE(R) 1950-2008/Nov 24
      (c) format only 2008 Dialog
*File 155:  NLM has suspended updating from 11/20-24/2008, as it begins
preparations for the annual reload.

      Set  Items  Description
      ---  -----  -----------
? s IL()6 and crp and cancer
          171027  IL
         2142376  6
           37229  IL()6
           14333  CRP
          667774  CANCER
      S1     130  IL()6 AND CRP AND CANCER
? s IL()6/ti and crp and cancer
           53893  IL/TI
           97606  6/TI
            4003  IL/TI()6/TI
           14333  CRP
```

```
        667774  CANCER
     S2      10  IL()6/TI AND CRP AND CANCER
? t s2/3,ab/all
```

2/3,AB/1
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

28156761 PMID: 18844497
Serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels in colorectal adenoma and cancer patients.
Grobelewska Magdalena; Mroczko Barbara; Wereszczynska-Siemiatkowska Urszula; Kedra Bogusław; Lukaszewicz Marta; Baniukiewicz Andrzej; Szmitkowski Maciej
Department of Biochemical Diagnostics, Medical University, Bialystok, Poland.
Clinical chemistry and laboratory medicine - CCLM/FESCC (Germany) 2008, 46 (10) p1423-8, ISSN 1434-6621--Print Journal Code: 9806306
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
BACKGROUND: Colorectal cancer is one of the most common cancers of the gastrointestinal tract and the fourth cause of cancer death in the world. It has been shown that local chronic inflammation may lead to colorectal carcinogenesis via adenomatous polyps. Interleukin-6 and C-reactive protein are biomarkers of inflammation and indicators of the immune response to tumors. METHODS: Serum levels of interleukin-6, carcinoembryonic antigen and carbohydrate antigen 19-9 were determined using immunoenzymatic assays, and C-reactive protein concentrations by immunoturbidimetric kits in 76 colorectal cancer patients before surgery, in 38 colorectal adenoma patients and in 35 healthy controls. RESULTS: Serum levels of interleukin-6, C-reactive protein and carcinoembryonic antigen were significantly higher in cancer patients when compared to adenoma patients and healthy subjects, and increased in more advanced stages of disease and in patients with non-resectable tumors. Based on Cox's analysis, the elevated preoperative serum level of C-reactive protein was an independent significant prognostic factor for patients' survival. CONCLUSIONS: Our findings suggest the usefulness of interleukin-6 in the diagnosis of colorectal cancer patients and C-reactive protein in the survival prognosis.

2/3,AB/2
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2008 Dialog. All rts. reserv.

16437355 PMID: 15955385
Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6.
Park Hye Soon; Park Jung Yul; Yu Rina
Department of Family Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, South Korea. hyesoon@amc.seoul.kr
Diabetes research and clinical practice (Ireland) Jul 2005, 69 (1) p29-35, ISSN 0168-8227--Print Journal Code: 8508335
Publishing Model: Print-Electronic
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
OBJECTIVE: To investigate the relationship between serum concentrations of the cytokines C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6, and obesity and visceral adiposity. METHODS: A cross-sectional study of 100 Korean adults free from pre-existing inflammatory disease or cancer was performed. Body mass index (BMI), waist circumference, and serum concentrations of CRP, TNF-alpha and IL-6 were measured. In 46 obese subjects, fat mass was assessed by bioimpedance analysis and abdominal fat distribution was determined by computerized tomography scan. RESULTS: Overall, serum concentrations of CRP, TNF-alpha and IL-6 were significantly correlated with weight, BMI, waist circumference, hip circumference, and waist-hip ratio. In obese subjects, CRP and IL-6 were significantly correlated with BMI, waist circumference and visceral adipose tissue. Multiple regression analysis showed that CRP was significantly associated with BMI, whereas IL-6 was significantly related with visceral adiposity in obese subjects. CONCLUSIONS: The positive associations of obesity and visceral adiposity with elevated cytokine levels suggest the importance of reducing obesity and visceral adiposity to prevent elevations in cytokine levels.

2/3,AB/3

16300615 PMID: 15786541
Serum IL-6, TNFalpha and CRP levels in Greek colorectal cancer patients: prognostic implications.
Nikiteas Nikolaos I; Tzanakis Nikolaos; Gazouli Maria; Rallis George; Daniilidis Kessaris; Theodoropoulos George; Kostakis Alkiviadis; Peros George
2nd Propedeutic Department of Surgery, School of Medicine, University of Athens, Athens 11527, Greece. nnkit@med.uoa.gr
World journal of gastroenterology - WJG (China) Mar 21 2005, 11 (11) p1639-43, ISSN 1007-9327--Print Journal Code: 100883448
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
AIM: The significance of preoperative serum IL-6, TNFalpha and CRP levels in the progression of colorectal cancer (CRC) has not been fully elucidated. Our intention was to investigate their role and identify their prognostic significance. METHODS: The IL-6, TNFalpha and CRP levels were measured in 74 CRC patients and the relationships between their elevations and both the clinicopathological factors and prognosis of patients were investigated. Serum concentrations of human IL-6 and TNFalpha were determined by enzyme-linked immunosorbent assay (ELISA). CRP was measured by an immunoturbidimetric method. RESULTS: Median IL-6, TNFalpha and CRP levels were significantly higher in CRC patients than in normal controls. High levels of serum IL-6, TNFalpha and CRP were correlated with larger tumor size. Furthermore, high IL-6 and high CRP levels were associated with reduced overall survival. CONCLUSION: Serum IL-6, TNFalpha and CRP levels definitely increase in CRC patients. Pre-operative serum elevation of IL-6 and CRP was thus found to be predictor of the prognosis of CRC patients. The clinical value of TNFalpha in CRC needs to be further investigated.

2/3,AB/4

15916569 PMID: 15309885
C-reactive protein as a prognostic variable that reflects uncontrolled up-regulation of the IL-1-IL-6 network system in colorectal carcinoma.
Miki Chikao; Konishi Naomi; Ojima Eiki; Hatada Tsuyoshi; Inoue Yasuhiro; Kusunoki Masato
Second Department of Surgery, Mie University School of Medicine, Mie, Japan.
Digestive diseases and sciences (United States) Jun 2004, 49 (6) p970-6, ISSN 0163-2116--Print Journal Code: 7902782
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Up-regulation of the IL-1-IL-6 network stimulates systemic expression of C-reactive protein (CRP). This cytokine network system plays a pivotal role in inducing angiogenic growth factors in intestinal mucosa. Serum CRP level and tissue concentrations of cytokines in colorectal cancer patients were determined and an in vitro model was employed to determine the time course of induction of IL-6 in Caco-2 cells. Increased serum CRP was associated with recurrent disease and shorter survival time. Intense surgical stress and the presence of an acute phase reactant were independently associated with overexpression of IL-6 in the tumor. Enhanced IL-6 protein expression in Caco-2 cells induced by the initial treatment with IL-1beta or lipopolysaccharide could be abrogated by additional presupplementation of IL-1ra. The presence of an acute phase reactant reflects uncontrolled up-regulation of the local IL-1-IL-6 network system in the tumor, which may enhance the survival and proliferation of remnant cancer cells after tumor resection.

2/3,AB/5

15552321 PMID: 14654926
Association of serum IL-6 levels with comprehensive geriatric assessment variables in a population of elderly cancer patients.
Mantovani Giovanni; Madeddu Clelia; Gramignano Giulia; Ferreli Luca; Massa Elena; Contu Paolo; Serpe Roberto
Department of Medical Oncology, University of Cagliari, Italy. mantovan@acs.unica.it

Oncology reports (Greece) Jan 2004, 11 (1) p197-206, ISSN 1021-335X --Print Journal Code: 9422756
Publishing Model: Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

The primary aim of this study was to find whether any association exists between serum levels of proinflammatory cytokines, mainly IL-6, and the most important comprehensive geriatric assessment (CGA) variables such as functional status, cognitive functions and nutrition in a population of elderly cancer patients. The secondary aims were to find whether any difference existed between: i) age groups, ii) performance status scores, iii) patients who had lost weight versus those who had not. Eighty-four elderly patients with advanced cancer were included in the study (stage III 15.4% and stage IV 72.6%). Serum levels of IL-6 and CRP were significantly higher in elderly than in the other adult cancer patients. Among the CGA variables investigated, the most affected were functional status assessed by IADL, cognitive functions by MMSE and nutrition. The ECOG PS was shown to be significantly associated with all the dimensions of CGA investigated: poor PS (>/=2) corresponded to severe disabilities. As for the relationship of serum IL-6 with CGA variables, the strongest correlations were between IL-6 and functional status assessed by both Katz ADL (p=0.0003), IADL (p=0.0070) and nutrition (p=0.0013). Moreover, we observed an association, although not statistically significant, between functional disability (ADL and IADL) and high IL-6 levels in individuals with weight loss. IL-6 levels seem to be independently associated with all CGA variables investigated in the present study in a population of elderly cancer patients. Because the most important CGA variables, in particular functional status, have been observed to be strongly associated with survival, the present study, confirming our previously reported ones, suggests that IL-6 may be a reliable marker of disease outcome and supports the feasibility of using IL-6 as a sensitive outcome marker in studies based on novel approaches aiming at modifying age- and cancer-related biologic mechanisms.

15446964 PMID: 14599731
Relationship of total and abdominal adiposity with CRP and IL-6 in women.
Rexrode Kathryn M; Pradhan Aruna; Manson Joann E; Buring Julie E; Ridker Paul M
Center of Cardiovascular Disease Prevention, Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215, USA. krexrode@partners.org
Annals of epidemiology (United States) Nov 2003, 13 (10) p674-82, ISSN 1047-2797--Print Journal Code: 9100013
Contract/Grant No.: CA-47988; CA; United States NCI; HL-43851; HL; United States NHLBI
Publishing Model: Print
Document type: Journal Article; Research Support, U.S. Gov't, P.H.S.
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed

PURPOSE: To examine the relationship between different measures of adiposity as predictors of C-reactive protein (CRP) and interleukin-6 (IL-6) levels. METHODS: A cross-sectional study of 733 women free from preexisting cardiovascular disease or cancer at baseline. MEASUREMENTS: Total adiposity, as measured by body mass index (BMI). Abdominal adiposity, as measured by waist circumference (WC) and waist/hip ratio (WHR), with sensitivity CRP levels and IL-6 levels. RESULTS: BMI, WHR, and WC were all significantly correlated with CRP and IL-6, throughout the anthropometric spectrum. After adjustment for risk factors, the odds ratios (ORs) were 12.2 (95% CI, 6.44-23.0) for elevated CRP (>/=75th percentile) and 4.13 (95% CI, 2.37-7.18) for elevated IL-6 (>/=75th percentile) in comparisons of extreme BMI quartiles. Among women in the highest WC quartile, the OR for elevated CRP and IL-6 were 8.57 (95% CI, 4.59-16.0) and 4.40 (95% CI, 2.46-7.89), while ORs for the highest WHR quartile were 2.88 (95% CI, 1.60-5.19) and 1.76 (95% CI, 1.03-3.01), respectively. Compared with lean nonusers, women in the highest BMI quartile who did not use hormone therapy (HT) had an OR for elevated CRP of 7.79 (95% CI, 2.08-29.2) vs. 31.6 (95% CI, 7.97-125.6) for current hormone users. CONCLUSIONS: Indices of both total and abdominal adiposity were strongly associated with significant increased levels of CRP and IL-6. This association was evident across the entire spectrum of BMI.

13552360 PMID: 10769674
TNF alpha, IL-1 beta and IL-6 production by peripheral blood monocytes in patients with renal cell carcinoma.
Ikemoto S; Sugimura K; Yoshida N; Wada S; Yamamoto K; Kishimoto T
Department of Urology, Osaka City University Medical School, Japan.
Anticancer research (GREECE) Jan-Feb 2000, 20 (1A) p317-21, ISSN 0250-7005--Print Journal Code: 8102988
Publishing Model: Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Renal cell carcinoma (RCC) has been shown to be immunologically more labile than other types of cancer. In this study, we examined tumor necrosis factor alpha (TNF alpha), interleukin-1 beta (IL-1 beta) and interleukin-6 (IL-6) production of peripheral blood monocytes in 38 RCC patients. Monocytes were isolated from peripheral blood mononuclear cells by adherence to a plastic dish and cultured with lipopolysaccharide for 24 hours. The culture supernatant was obtained, and the production of TNF alpha, IL-1 beta and IL-6 was measured by ELISA. As a result, TNF alpha and IL-1 beta production was significantly higher in the high stage patients compared to the control subjects and low stage patients. When the patients were divided according to serum C-reactive protein (CRP), TNF alpha, IL-1 beta and IL-6 production was significantly higher in the CRP-positive patients compared to the control subjects and the CRP-negative patients. Overexpression of these cytokines may therefore induce a hypermetabolic status that may be a cause of malnutrition and cancer cachexia.

2/3, AB/8
DIALOG(R)File 155:MEDLINE(R)

13549669 PMID: 10768866
Effect of IL-6 elevation in malignant pleural effusion on hyperfibrinogenemia in lung cancer patients.
Yamaguchi T; Kimura H; Yokota S; Yamamoto Y; Hashimoto T; Nakagawa M; Ito M; Ogura T
Department of Internal Medicine, Toneyama National Hospital, Osaka, Japan.
Japanese journal of clinical oncology (JAPAN) Feb 2000, 30 (2) p53-8, ISSN 0368-2811--Print Journal Code: 0313225
Publishing Model: Print
Document type: Journal Article; Research Support, Non-U.S. Gov't
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
BACKGROUND: The involvements of interleukin-6 (IL-6) and fibrinogen in cancer development were elucidated independently, irrespective of IL-6 activity to induce fibrinogen. This study was undertaken to clarify the clinicopathological association of these molecules in lung cancer patients with malignant pleurisy. METHODS: IL-6, fibrinogen and the related molecules in blood and pleural effusion of 38 patients were assayed at 3-day intervals. RESULTS: IL-6 levels were elevated in sera of 27 cases (71.1%) and in all the effusions with mean values of 20.5 and 9970.5 pg/ml, respectively. Their correlation in 22 cases who were examined on the same day was statistically strong ($r = 0.902$, $p < 0.0001$). Occasional elevations of tumor necrosis factor-alpha were independent of IL-6 elevation. Levels of plasma fibrinogen, fibrin(ogen) degradation products (FDP) and C-reactive protein (CRP) were more frequently elevated in the IL-6-elevated cases than those without IL-6 elevation. In all pleural effusions, fibrinogen levels were significantly decreased to <150 mg/dl with large elevations of FDP level. Immunocytologically, IL-6 was detected in cancer cells in 16 cases of adenocarcinoma in addition to host pleural cells, but its cellular positivity was not reflected in the IL-6 level in each pleural effusion. CONCLUSION: Compared with lung cancer patients without malignant pleurisy, IL-6, fibrinogen, FDP and CRP levels in patients with malignant pleurisy were increased more frequently in their peripheral blood. These were basically attributed to systemic leakage of IL-6 from the affected pleural cavity, in which plasma fibrinogen induced in response to serum IL-6 was exudated and degraded predominantly to FDP.

2/3, AB/9
DIALOG(R)File 155:MEDLINE(R)

13536952 PMID: 10749586
CRP, TNF-alpha, IL-1ra, IL-6, IL-8 and IL-10 in blood serum of colorectal cancer patients.

Kaminska J; Kowalska M M; Nowacki M P; Chwalinski M G; Rysinska A; Fuksiewicz M.
Maria-Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Department of Tumor Markers, Roentgen 5, Warsaw, 02-781, Poland.
Pathology oncology research - PCR (HUNGARY) 2000, 6 (1) p38-41, ISSN 1219-4956--Print
Journal Code: 9706087
Publishing Model: Print
Document type: Comparative Study; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Blood serum cytokines: TNFalpha, IL-1ra, IL-6, IL-8, IL-10 as well as CRP were investigated in patients with colorectal **cancer**, prior treatment and 1, 10 and 42 days after surgery. There was an increase of the levels of CRP, IL-6 and IL-10 in most patients 24 hours after surgery. The levels of IL-1ra were elevated in patients in stage C and in several patients in stage B of the disease and there was a decrease of circulating TNFalpha in stage B patients. On day 10 and 42 after surgery, the levels of cytokines followed various patterns.

2/3, AB/10
DIALOG(R)File 155:MEDLINE(R)

11495814 PMID: 7579407
Measurement of whole body interleukin-6 (**IL-6**) production: prediction of the efficacy of anti-**IL-6** treatments.
Lu Z Y; Brailly H; Wijdenes J; Bataille R; Rossi J F; Klein B
Institute for Molecular Genetics, CNRS BP5051, Montpellier, France.
Blood (UNITED STATES) Oct 15 1995, 86 (8) p3123-31, ISSN 0006-4971--Print
Journal Code: 7603509
Publishing Model: Print
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
A major limitation on the therapeutic use of cytokine antagonists is that the amount of cytokine to be neutralized in vivo is not presently known. We previously reported that anti-interleukin-6 (IL-6) monoclonal antibody (MoAb) administered to a patient with multiple myeloma (MM) induced high amounts of IL-6 to circulate in the form of monomeric immune complexes. Based on this observation, the present study developed a new methodology to estimate daily IL-6 production in 13 patients with MM or renal **cancer** who received anti-IL-6 MoAb. Treatment was considered effective when the production of C-reactive protein (**CRP**) was inhibited. The production of this acute-phase protein by hepatocytes is dependent on the activation of IL-6 gp130 transducer. Inhibition of tumor proliferation was also evaluated in patients with MM. In 7 of 13 patients whose **CRP** production was completely inhibited (> 96%) and who showed some antitumoral effects, whole-body IL-6 production in vivo was less than 18 micrograms/d (median, 5.7 micrograms/d; range, 0.5 to 17.5 micrograms/d). In the other 6 patients, subtotal inhibition of **CRP** production and a lack of antitumoral response were associated with high IL-6 production (median, 180 micrograms/d; range, 18 to 358 micrograms/d). These in vivo observations were consistent with mathematical modeling that predicted that anti-IL-6 MoAb treatment would be efficient only in low IL-6 producers. These data indicate the difficulty of neutralizing IL-6 with a single anti-IL-6 MoAb in vivo and call for new strategies to avoid accumulation of IL-6 in the form of stable immune complexes.
? logof
>>>Invalid set number
? logout
02dec08 15:01:43 User217743 Session D745.4
$4.03 1.146 DialUnits File155
$2.40 10 Type(s) in Format 4 (UDF)
$2.40 10 Types
$6.43 Estimated cost File155
$0.80 TELNET
$7.23 Estimated cost this search
$17.07 Estimated total session cost 4.692 DialUnits
Logoff: level 05.22.00 D 15:01:43

Connecting via Winsock to Dialog

Logging in to Dialog

Trying 31060000009998...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:

10/614481 09/07/2006

```
 ********
ENTER PASSWORD:
 ********
Welcome to DIALOG

Dialog level 05.22.00D

Last logoff:  02dec08 15:01:43
Logon file405 02dec08 15:16:53
>>>PROFILE is in a suspended state.
>>>Contact Dialog Customer Services to re-activate it.
* * *
SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.8.0 term=ASCII
                      *** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
  1.  Announcements (new files, reloads, etc.)
  2.  Database, Rates, & Command Descriptions
  3.  Help in Choosing Databases for Your Topic
  4.  Customer Services (telephone assistance, training, seminars, etc.)
  5.  Product Descriptions

 Connections:
  6.  DIALOG(R) Document Delivery
  7.  Data Star(R)

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      /H = Help            /L = Logoff            /NOMENU = Command Mode


Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B 1 for ERIC).
? b 410

       02dec08 15:16:54 User217743 Session D746.1
          $0.00      0.267 DialUnits FileHomeBase
     $0.00  Estimated cost FileHomeBase
     $0.00  Estimated cost this search
     $0.00  Estimated total session cost    0.267 DialUnits

File 410:Dialog Comm-of-Interest Newsletters 2008/Mar
       (c) 2008 Dialog

      Set  Items  Description
      ---  -----  -----------
? set hi ;set hi
HILIGHT set on as ''
HILIGHT set on as ''
? b 155
       02dec08 15:16:58 User217743 Session D746.2
          $0.00      0.117 DialUnits File410
     $0.00  Estimated cost File410
     $0.02  TELNET
     $0.02  Estimated cost this search
     $0.02  Estimated total session cost    0.384 DialUnits

File 155:MEDLINE(R) 1950-2008/Nov 24
       (c) format only 2008 Dialog
*File 155:  NLM has suspended updating from 11/20-24/2008, as it begins
preparations for the annual reload.

      Set  Items  Description
      ---  -----  -----------
? s (reduce or reduction) adj2 inflammatory adj markers
>>>Invalid syntax
? s (reduce or reduction) with inflammatory()markers
>>>Invalid syntax
? s (reduce or reduction) and inflammatory()markers
          230294  REDUCE
          569508  REDUCTION
          310015  INFLAMMATORY
          295160  MARKERS
            3397  INFLAMMATORY(W)MARKERS
      S1     428  (REDUCE OR REDUCTION) AND INFLAMMATORY()MARKERS
? s s1 and c()reactive()protein
             428  S1
         1207816  C
          167884  REACTIVE
         1863179  PROTEIN
           25278  C(W)REACTIVE(W)PROTEIN
```

10/614481 09/07/2006

```
      S2          206  S1 AND C()REACTIVE()PROTEIN
? s s2 and IL()6
                206  S2
         171027  IL
        2142376  6
          37229  IL(W)6
      S3          56  S2 AND IL()6
? s s3 and il()6/ti
                56  S3
          53893  IL/TI
          97606  6/TI
           4003  IL/TI(W)6/TI
      S4           0  S3 AND IL()6/TI
? s s2/ti
      S5          86  S2/TI
? s s3 and s5
                56  S3
                86  S5
      S6          25  S3 AND S5
? t s6/ti,ab/all

 6/TI,AB/1
DIALOG(R)File 155:(c) format only 2008 Dialog. All rts. reserv.

   Interleukin-6 is a better predictor of mortality as compared to C-
reactive protein, homocysteine, pentosidine and advanced
oxidation protein products in hemodialysis patients.
   Inflammatory markers predict mortality in hemodialysis (HD)
patients, whereas a possible association between oxidative stress (OS)
markers and survival is less clear. We assessed the impact on all-cause
mortality of baseline inflammatory [high-sensitivity C-reactive
protein, and interleukin-6 (IL-6)] and OS markers
(advanced oxidation protein products, pentosidine, homocysteine) in 112 HD
patients. We found no significant correlations between inflammatory and OS
markers. During the 5.5 years of follow-up, 51 patients died. In a
Kaplan-Meier analysis, the survival rate was reduced in patients with
IL-6 higher than the median (IL-6 >4.2 pg/ml) (log-
rank = 6.47; p = 0.01), in diabetics (log-rank = 12.26; p = 0.0005) and in
older patients (log-rank = 11.22; p = 0.0008). Moreover, in Cox analysis
only IL-6 and age were independently associated with mortality.
We conclude that in this group of prevalent Brazilian HD patients, IL
-6 was a better predictor of survival than other inflammatory and OS
markers. Copyright 2008 S. Karger AG, Basel.


 6/TI,AB/2
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   Effect of psyllium fiber supplementation on C-reactive
protein: the trial to reduce inflammatory markers
(TRIM).
   PURPOSE: Recent evidence supports a significant association between the
intake of dietary fiber and levels of inflammatory markers. The
objective of this study was to determine whether daily fiber
supplementation would reduce levels of inflammatory
markers. METHODS: This study was a prospective randomized controlled
trial at a single university medical center. Participants were overweight
or obese adults with no history of heart disease. The intervention was
psyllium supplementation at either 7 or 14 g/d for 3 months compared with
no supplements in a control group. The main outcome measure was change in
level of high-sensitivity C-reactive protein (hsCRP)
concentration; secondary outcomes included changes in interleukin-6 (
IL-6) levels, fibrinogen levels, and white blood cell (WBC)
count. Protocol completers attended at least 2 visits and took more than
75% of the prescribed fiber dose. RESULTS: In this intent-to-treat analysis
(n = 158), there were no significant differences between either of the 2
treatment groups and the control group in the amount of change in CRP,
fibrinogen, or IL-6 levels or in WBC count (P>.05). In the
analysis of protocol completers (n = 132), there also were no significant
differences between the groups except for a small decrease in fibrinogen
level in the high-fiber group (-6 mg/dL [-0.18 micromol/L] compared with 13
mg/dL [0.38 micromol/L] in the control group, P<.05). CONCLUSION: Psyllium
fiber supplementation did not significantly reduce CRP levels in
overweight or obese individuals in this trial, and changes in other markers
were not consistent. Further research is needed to determine whether other
fibers or nutrients can reduce inflammatory markers.


 6/TI,AB/3
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   Xuezhikang, an extract of cholestin, decreases plasma inflammatory
markers and endothelin-1, improve exercise-induced ischemia and
subjective feelings in patients with cardiac syndrome X.
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Previous studies have demonstrated that Xuezhikang, an extract of cholestin, available from Chinese red yeast rice, could effectively modify lipid profile. The present study was undertaken to investigate whether Xuezhikang could modify endothelin-1 (ET-1), interleukin-6 (IL-6), high-sensitivity C-reactive protein (CRP) and exercise-induced ischemia in patients with cardiac syndrome X (CSX). Thirty-six patients with CSX were randomly assigned to 1200 mg/d of Xuezhikang or placebo group (n=18 respectively). Blood samples were drawn at day 0 and day 90 for measuring above parameters. The treadmill exercise tests and subjective feelings were also assessed at day 0 and day 90. The data showed that Xuezhikang therapy resulted in significant reductions in total cholesterol (TC, 19%), low-density lipoprotein cholesterol (LDL-C) (26%), and triglycerides (TG) compared with baseline (16% p<0.01 respectively). The data also showed that Xuezhikang led significantly to reductions in median and log-CRP levels (38% and 44% p<0.01 respectively), IL-6 (20% p<0.01), and ET-1 (47% p<0.01) compared with baseline. The exercise duration, and time to 1 mm ST-segment depression was significantly prolonged after Xuezhikang therapy (9% and 6% p<0.05 respectively) accompanied by improvement of subjective feelings. Data suggested that the benefit of Xuezhikang resulted in significant modification vascular function by reduction of ET-1, inflammatory markers and LDL cholesterol, which may be clinically important for patients with CSX.

6/TI, AB/4
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Effect of tiotropium on sputum and serum inflammatory markers and exacerbations in COPD.

Chronic obstructive pulmonary disease (COPD) patients experiencing frequent exacerbations demonstrate increased stable-state airway inflammation. Tiotropium has been shown to reduce exacerbation frequency, but its effect on airway inflammation is unknown. The aim of the present study was to investigate the effect of tiotropium on sputum inflammatory marker and exacerbation frequency. Patients (n = 142) were randomised to receive tiotropium or placebo in addition to their usual medication for 1 yr. Sputum and serum cytokines were assayed by ELISA and exacerbation frequency calculated using a symptom-based diary. There was no difference in the area under the curve for sputum interleukin (IL)-6 or myeloperoxidase between the groups, but sputum IL-8 level was increased in the tiotropium arm. There was no difference between start and end of study in serum IL-6 or C-reactive protein level. Tiotropium was associated with a 52% reduction in exacerbation frequency (1.17 versus 2.46 exacerbations.yr(-1)). Of patients on tiotropium, 43% experienced at least one exacerbation, compared with 64% on placebo. The total number of exacerbation days was reduced compared with placebo (17.3 versus 34.5 days). Tiotropium reduces exacerbation frequency in chronic obstructive pulmonary disease, but this effect does not appear to be due to a reduction in airway or systemic inflammation.

6/TI, AB/5
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The effect of testosterone replacement therapy on adipocytokines and C-reactive protein in hypogonadal men with type 2 diabetes.

OBJECTIVE: Serum testosterone levels are known to inversely correlate with insulin sensitivity and obesity in men. Furthermore, there is evidence to suggest that testosterone replacement therapy reduces insulin resistance and visceral adiposity in type 2 diabetic men. Adipocytokines are hormones secreted by adipose tissue and contribute to insulin resistance. We examined the effects of testosterone replacement treatment on various adipocytokines and C-reactive protein (CRP) in type 2 diabetic men. DESIGN: Double-blinded placebo-controlled crossover study in 20 hypogonadal type 2 diabetic men. Patients were treated with testosterone (sustanon 200 mg or placebo) intramuscularly every 2 weeks for 3 months in random order followed by a washout period of 1 month before the alternate treatment phase. METHODS: Leptin, adiponectin, resistin, tumour necrosis factor-alpha (TNF-alpha), interleukin (IL)-6 and CRP levels were measured before and after each treatment phase. Body mass index (BMI) and waist circumference were also recorded. RESULTS: At baseline, leptin levels significantly correlated with BMI and waist circumference. There was a significant inverse correlation between baseline IL-6 and total testosterone (r=-0.68; P=0.002) and bioavailable testosterone levels (r=-0.73; P=0.007). CRP levels also correlated significantly with total testosterone levels (r=-0.59; P=0.01). Testosterone treatment reduced leptin (-7141.9 +/- 1461.8 pg/ml; P=0.0001) and adiponectin levels (-2075.8 +/- 852.3 ng/ml; P=0.02). There was a significant reduction in waist circumference. No significant effects of testosterone therapy on resistin, TNF-alpha, IL-6 or CRP levels were observed. CONCLUSION: Testosterone replacement treatment decreases leptin and adiponectin levels

in type 2 diabetic men. Moreover, low levels of testosterone in men are associated with pro-inflammatory profile, though testosterone treatment over 3 months had no effect on inflammatory markers.

6/TI,AB/6
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School-based intervention acutely improves insulin sensitivity and decreases inflammatory markers and body fatness in junior high school students.
CONTEXT: Risk factors for type 2 diabetes mellitus (T2DM) include obesity, family history, dyslipidemia, a proinflammatory state, impaired insulin secretory capacity, and insulin resistance. OBJECTIVE: The aim of this study was to examine the effects of a 3- to 4-month school-based intervention consisting of health, nutrition, and exercise classes plus an aerobic exercise program on diabetes risk. DESIGN: This study was a randomized, before/after, controlled trial. METHODS: Seventy-three eighth-grade students in a predominantly Hispanic New York City public school were divided into a control group (studied twice without receiving the intervention) and an experimental group (studied before and after the intervention). OUTCOME MEASURES: We measured body fatness (bioelectrical impedance), insulin sensitivity, beta-cell function (insulin release in response to an iv glucose load corrected for insulin sensitivity), lipid profiles, and circulating concentrations of IL-6, C-reactive protein, adiponectin, and TNF-alpha. RESULTS: Participation in the intervention was associated with significant reductions in body fatness, insulin resistance, and circulating concentrations of C-reactive protein and IL-6, irrespective of somatotype on enrollment. CONCLUSION: Short-term school-based health, nutrition, and exercise intervention is beneficial to all students and affects multiple diabetes risk factors.

6/TI,AB/7
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The effects of short term (3 weeks) testosterone treatment on serum inflammatory markers in men undergoing coronary artery stenting.
OBJECTIVE: Inflammation markers can predict restenosis after successful intracoronary stenting. There is evidence that testosterone suppresses the expression of the inflammatory cytokines. We hypothesized that testosterone therapy after coronary stenting can reduce the inflammation markers.
METHODS: We selected 41 men with coronary artery disease who underwent successful stent implantation for a >70% diameter stenosis of a major coronary artery. Patients, who had stable angina and positive exercise test results, were recruited after diagnostic coronary angiography. Twenty-five men were treated with 3 doses of i.m testosterone administration once a week for 3 weeks following diagnostic angiography. Sixteen patients were recruited as a control group and they received standard therapy. First venous blood samples were obtained after angiography. Stents were implanted 3 weeks after diagnostic angiography. Second venous blood samples were taken 24 h after the coronary stenting. RESULTS: Baseline biochemical or hematological parameters were similar between the control and treatment groups. After coronary stenting, free testosterone, total testosterone, and sex hormone binding globulin were significantly elevated in the testosterone group (P<0.0001, P<0.0001 and P=0.02; respectively). After coronary stent implantation, there was a significant increase in IL-6 and CRP levels in the control group only (P=0.02 and P=0.038), while TNF-alpha levels were increased significantly in both groups (P=0.016 and P=0.014; respectively). Statistical analysis revealed that testosterone treatment prior to stent implantation attenuated IL-6 and hs-CRP levels significantly (P=0.042 and P=0.043; respectively). CONCLUSIONS: The present study shows that 3 weeks testosterone treatment prior to intracoronary stenting results in a significant suppression in hs-CRP and IL-6 levels after the stent implantation.

6/TI,AB/8
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Interleukin-6 -174 G/C promoter polymorphism and effects of fenofibrate and simvastatin on inflammatory markers in hypercholesterolemic patients.
To evaluate whether the interleukin-6 (IL-6) -174 G/C polymorphism might alter the effects of micronized fenofibrate or simvastatin therapy on inflammatory markers, we measured IL-6, C-reactive protein, CD40 ligand, adhesion molecules, P-selectin and monocyte chemoattractant protein-1 in hypercholesterolemic patients both before and after a 30-day treatment. Serum IL-6 levels were significantly higher in patients with the GC or CC genotypes (P=0.04). The presence of the C allele was associated with greater absolute reduction of IL-6 levels

(P=0.04) following fenofibrate treatment. There was no significant association between the -174 G/C IL-6 polymorphism and the effects of simvastatin treatment. A relationship between the -174 G/C IL-6 polymorphism and the anti-inflammatory action of fenofibrate reported might be useful in the optimization of the treatment regimen in patients receiving this class of drugs.

6/TI,AB/9
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Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects.
Obesity is associated with low-grade inflammation, insulin resistance, type 2 diabetes, and cardiovascular disease. This study investigated the effect of a 15-wk lifestyle intervention (hypocaloric diet and daily exercise) on inflammatory markers in plasma, adipose tissue (AT), and skeletal muscle (SM) in 27 severely obese subjects (mean body mass index: 45.8 kg/m2). Plasma samples, subcutaneous abdominal AT biopsies, and vastus lateralis SM biopsies were obtained before and after the intervention and analyzed by ELISA and RT-PCR. The intervention reduced body weight (P < 0.001) and increased insulin sensitivity (homeostasis model assessment; P < 0.05). Plasma adiponectin (P < 0.001) increased, and C-reactive protein (P < 0.05), IL-6 (P < 0.01), IL-8 (P < 0.05), and monocyte chemoattractant protein-1 (P < 0.01) decreased. AT inflammation was reduced, determined from an increased mRNA expression of adiponectin (P < 0.001) and a decreased expression of macrophage-specific markers (CD14, CD68), IL-6, IL-8, and tumor necrosis factor-alpha (P < 0.01). After adjusting for macrophage infiltration in AT, only IL-6 mRNA was decreased (P < 0.05). Only very low levels of inflammatory markers were found in SM. The intervention had no effect on adiponectin receptor 1 and 2 mRNA in AT or SM. Thus hypocaloric diet and increased physical activity improved insulin sensitivity and reduced low-grade inflammation. Markers of inflammation were particularly reduced in AT, whereas SM does not contribute to this attenuation of whole body inflammation.

6/TI,AB/10
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Endurance training reduces circulating inflammatory markers in persons at risk of coronary events: impact on plaque stabilization?
Inflammatory pathways are involved in destabilization of atherosclerotic plaques. We assessed the hypothesis that endurance training decreases circulating concentrations of inflammatory markers in persons with coronary artery disease (CAD) and cardiovascular risk factors (CVRFs). Thirty-two subjects with CAD and/or CVRFs joined a 12-week supervised endurance training. We found a significant decrease of the chemokines interleukin (IL)-8 (pre: 3.9+/-0.6, change: -1.2+/-0.4 pg/ml, -21% p=0.002) and monocyte chemoattractant protein-1 (pre: 213+/-9, change: -20.4+/-8.2 pg/ml, -5% p=0.03). Diabetes mellitus (DM) significantly influenced changes of IL-8 (p=0.002). IL-8 substantially dropped by 39% in diabetics. Moreover, matrix metalloproteinase-9 (MMP-9) highly significantly decreased in response to training (pre: 750+/-98, change: -278+/-77 ng/ml, -18% p=0.005). Exercise-induced changes of MMP-9 were influenced by concomitant use of statins (p=0.038). We observed a particularly strong MMP-9 reduction of 44% in patients treated with statins. Acute phase reactants IL-6 (pre: 1.7+/-0.3, change: +0.25+/-0.7 pg/ml, +4% p=0.58) and high sensitivity C-reactive protein (pre: 2.1+/-0.5, change: -0.25+/-0.4 mg/l, -9% p=0.54) did not change in response to training. In conclusion, endurance training decreased circulating chemokines and MMP-9, which may in part explain its beneficial effect on coronary risk. Patients with DM or treated with statins because of hypercholesterolemia may particularly take advantage.

6/TI,AB/11
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Changes of plasma inflammatory markers after withdrawal of statin therapy in patients with hyperlipidemia.
BACKGROUND: Atherosclerosis has been considered to be an inflammatory process. In addition to its lipid-lowering properties, statin has been shown to decrease the concentrations of inflammatory markers resulting in reduction of cardiovascular events. Emerging data suggest that withdrawal of statin might be associated with increased cardiac events. The mechanism for this phenomenon, however, is still unclear. We investigated whether acute termination of statin treatment could result in rebound of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), in patients with hyperlipidemia. METHODS: Seventeen patients (11 men and 6 women, mean age 51+/-7 years) with hyperlipidemia were given 40

mg/day of pravastatin for 6 weeks. The concentrations of plasma CRP and IL-6 were evaluated before receiving the statin therapy, immediately after 6 weeks of pravastatin therapy, and at days 1, 3 and 7 after withdrawal of pravastatin therapy. The lipid profile was also evaluated at baseline, 6 weeks of therapy, and at day 7 after terminating pravastatin. RESULTS: Pravastatin therapy induced significant reductions in total cholesterol (TC, 6.88+/-0.36 vs. 5.27+/-0.23 mmol/l, p<0.01), low-density lipoprotein (LDL) cholesterol (4.28+/-0.25 vs. 3.06+/-0.14 mmol/l, p<0.01), CRP (0.28+/-0.16 vs. 0.20+/-0.08 mg/l, p<0.01), and IL-6 (8.4+/-0.6 vs. 6.7+/-0.4 pg/dl, p<0.01). Although the TC and LDL-cholesterol did not change during the 7-day period after withdrawal of pravastatin therapy, the concentrations of CRP and IL-6 increased at day 3 (CRP: 0.20+/-0.08 vs. 0.27+/-0.12 mg/l, and IL-6: 6.7+/-0.4 vs. 7.7+/-0.6 pg/dl, p<0.05 respectively) and at day 7 (CRP: 0.20+/-0.08 vs. 0.30+/-0.14 mg/l, and IL-6: 6.7+/-0.4 vs. 8.7+/-0.8 pg/dl, p<0.01 respectively) after withdrawal of pravastatin therapy. No correlation between increase of CRP as well as IL-6 and small changes of LDL-cholesterol concentrations was found after withdrawal of pravastatin therapy at day 7 (r=-0.021 and r=-0.044 respectively, p>0.05 respectively). CONCLUSIONS: 6 weeks after pravastatin therapy could significant modify the lipid profile and decrease the inflammatory markers including CRP and IL-6 in patients with hypercholesterolemia. Moreover, statin therapy discontinuation could induce a rebound phenomenon of inflammatory response representing an increase in some inflammatory markers, which is independent of changes of lipid parameters.

6/TI,AB/12
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The decrease in C-reactive protein concentration after diet and physical activity induced weight reduction is associated with changes in plasma lipids, but not interleukin-6 or adiponectin.

Subclinical inflammation is a risk factor for cardiovascular disease. The mechanisms underlying increased levels of inflammatory markers and their changes in response to weight loss are not fully understood yet. It has been proposed that elevated concentrations of C-reactive protein (CRP) are mediated by cytokines produced in adipose tissue. We investigated the changes in circulating CRP after weight reduction, in relation to parameters relevant to the metabolic syndrome. Forty 25- to 35-year-old obese female volunteers participated in an intervention program of dietary education and supervised physical activity for a period of 9 weeks. Anthropological parameters and biochemical measurements (high-sensitivity CRP [hsCRP], plasma lipoproteins, interleukin 6 [IL-6], adiponectin) were analyzed before and after the intervention. Body mass index decreased by more than 7% from 31.5 +/- 4.1 to 29.1 +/- 3.9. Plasma free fatty acid (FFA) concentrations decreased by 30%; high-density lipoprotein cholesterol increased by 8%; and fasting insulin concentrations decreased by 15%. There were no significant changes in either low-density lipoprotein cholesterol or triacylglycerol concentrations. Subcutaneous and visceral adipose tissue mass decreased by 12% and 18%. High-sensitivity CRP concentrations decreased by 30%; however, mean plasma IL-6 and adiponectin concentrations remained unchanged. In linear regression analysis, the changes in plasma hsCRP concentrations were associated with baseline hsCRP concentration, change in triacylglycerols and FFA concentrations, and in waist circumference. The decrease in hsCRP concentration after weight reduction does not appear to be mediated by decreases in circulating IL-6 or adiponectin concentrations; however, change in hsCRP concentration is related to changes in waist circumference and lipid metabolism reflected by plasma triacylglycerol and FFA levels.

6/TI,AB/13
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Effects of rosiglitazone on lipids, adipokines, and inflammatory markers in nondiabetic patients with low high-density lipoprotein cholesterol and metabolic syndrome.

BACKGROUND: PPAR-gamma agonists improve insulin sensitivity and glycemic control in type 2 diabetes and may reduce atherosclerosis progression. Thus, PPAR-gamma agonists may be an effective therapy for metabolic syndrome. However, the full spectrum of potentially antiatherogenic mechanisms of PPAR-gamma agonists have not been fully tested in nondiabetic patients with metabolic syndrome. METHODS AND RESULTS: We performed a prospective, double-blinded, placebo-controlled study of 60 nondiabetic subjects with low high-density lipoprotein cholesterol (HDL-C) level and metabolic syndrome to rosiglitazone 8 mg daily or placebo for 12 weeks. We found no significant effect of rosiglitazone on HDL-C (+5.5% versus +5.8%, P=0.89), and an increase in total cholesterol (+8% versus -1%, P=0.03). Nevertheless, rosiglitazone significantly increased adiponectin (+168% versus +25%, P<0.001), and lowered resistin (-6% versus +4%, P=0.009), C-reactive

protein (-32% versus +36% P=0.002), interleukin (IL)-**6** (-22% versus +4% P<0.001), and soluble tumor-necrosis factor-alpha receptor-2 (-5% versus +7% P<0.001). CONCLUSIONS: These findings suggest that rosiglitazone, presumably through its PPAR-gamma agonist properties, has direct effects on **inflammatory** markers and adipokines in the absence of favorable lipid effects. These findings may help explain the mechanism underlying the possible antiatherosclerotic effects of rosiglitazone.

6/TI,AB/14
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In vivo and in vitro effects of simvastatin on **inflammatory** markers in pre-dialysis patients.
BACKGROUND: The beneficial effects of statins in reducing cardiovascular events have been attributed predominantly to their lipid-lowering effects, recent studies suggest that these effects might be due to their anti-inflammatory properties. We here investigate the in vivo and in vitro effects of simvastatin on cytokine production in pre-dialysis chronic renal failure patients. METHODS: Our clinical study has been designed as a randomized double-blind placebo controlled study. A total of 55 chronic kidney disease (CKD) patients at stages 3 and 4 (mean creatinine clearance 45 ml/min, range 15-60) were randomly assigned to receive simvastatin 40 mg/day or placebo, added to their ongoing treatment, for 6 months. Blood samples were obtained at baseline, and after 3 and 6 months of observation for the determination of lipids, **inflammatory** markers and renal function. For the in vitro studies, the effect of increasing doses of simvastatin on cytokine production [namely interleukin (IL)-**6** and IL-8] in human cultured monocytes from 10 healthy subjects (HS) and 15 CKD patients stimulated by lipopolysaccharide (LPS) was investigated. RESULTS: A significant **reduction** in total cholesterol from 221+/-44 mg/dl to 184+/-41 mg/dl (3 months) and to 186+/-39 mg/dl (6 months) (P<0.02) and low-density lipoprotein cholesterol from 139+/-40 mg/dl to 104+/-29 mg/dl (3 months) and to 100+/-31 mg/dl (6 months) (P<0.001) was observed in the 28 patients treated with simvastatin. In this group, **C-reactive protein** (CRP) levels significantly decreased from 2.6 mg/l [interquartile range (IQR 4.9)] to 2.0 mg/l (IQR 1.9) (P = 0.03) at 6 months (P<0.05). A parallel **reduction** of IL-**6** levels from 5.1 pg/ml (IQR 3.6) to 3.5 pg/ml (IQR 3.1) (P = 0.001) at 6 months was also observed. No significant **reduction** in **inflammatory** markers [CRP from 5.1 mg/l (IQR 1.9) to 5.4 mg/l (IQR 1.3) (P = NS) at 6 months] or plasma lipids [LDL-cholesterol from 127+/-32 mg/dl to 131+/-21 mg/dl (6 months)] was observed in the 27 patients of the placebo group. In the in vitro studies, the average value for cell-associated IL-**6** and IL-8 was higher in CKD (155+/-95 pg/ml monocytes for IL-**6** and 722+/-921 pg/ml monocytes for IL-8) vs HS (37+/-87 pg/ml monocytes and 186+/-125 pg/ml monocytes) (P<0.01) and was not affected by simvastatin alone. LPS resulted in a significant increase in cytokine production (IL-**6**: 1954+/-321 pg/ml monocytes for CKD and 1451+/-237 pg/ml monocytes for HS; P<0.001); the simultaneous addition of increasing doses of simvastatin to these cultures induced a dose-dependent inhibition of IL-**6** and IL-8 production in stimulated peripheral blood mononuclear cells in all groups. CONCLUSIONS: These results indicate that simvastatin in commonly used doses has an in vitro and in vivo anti-inflammatory effect in CKD patients, and may play an important role in counteracting the mechanisms involved on the pathogenesis of cardiovascular disease.

6/TI,AB/15
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CRP **reduction** following gastric bypass surgery is most pronounced in insulin-sensitive subjects.
OBJECTIVE: Obesity is frequently associated with insulin resistance, dyslipidemia, hypertension and an increased risk of cardiovascular disease, reflected in elevated markers of inflammation, in particular **C-reactive protein** (CRP). To what extent the insulin resistance or the obesity per se contributes to increased CRP levels is unclear. In morbidly obese patients, gastric bypass surgery causes marked changes in body weight and improves metabolism thereby providing informative material for studies on the regulation of **inflammatory** markers. DESIGN: Prospective, surgical intervention study of **inflammatory** markers in morbidly obese subjects. SUBJECTS: In total, 66 obese subjects with mean age 39 y and mean body mass index (BMI) 45 kg/m2 were studied prior to and 6 and 12 months following Roux-en-Y gastric bypass (RYGBP) surgery. MEASUREMENTS: Serum concentrations of high sensitivity CRP, serum amyloid A (SAA) and interleukin-6 (IL-6), as well as markers of glucose and lipid metabolism RESULTS: Prior to surgery, CRP levels were elevated compared to the reference range of healthy, normal-weight subjects. CRP correlated with insulin sensitivity, as reflected by the homeostatic model assessment (HOMA) index, but not BMI, when corrected for age and gender. Surgery reduced BMI from 45 to 31 kg/m2

and lowered CRP, SAA and **IL-6** levels by 82, 57 and 50% respectively, at 12 months. The **reduction** in CRP was inversely related to HOMA at baseline independently of the change in body weight (r=-0.36, P=0.005). At 12 months, 140 and 40% reductions in CRP were seen in subjects with HOMA < 4 (insulin sensitive) and HOMA>9 (insulin resistant) despite similar reductions in BMI. Reductions in SAA and IL-6 tended to parallel the changes in CRP but were less informative. CONCLUSION: In morbidly obese subjects, gastric bypass surgery lowers energy intake, reduces **inflammatory markers** and improves insulin sensitivity. Despite a marked **reduction** in body weight, only a small effect on CRP levels was seen in insulin-resistant patients, indicating that flexibility of circulating CRP levels is primarily dependent upon insulin sensitivity rather than energy supply.

6/TI,AB/16
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The effect of orlistat-induced weight loss on interleukin-6 and C-**reactive protein** levels in obese subjects.
OBJECTIVE: Inflammation plays a major role in the pathogenesis of atherosclerosis. Obesity is an independent risk factor for cardiovascular disease, which may be mediated by increased secretion of proinflammatory cytokines by adipose tissue. The aim of this study is to investigate changes in the **inflammatory markers** interleukin-6 (**IL-6**) and high-sensitivity C-**reactive protein** (hs-CRP) during weight **reduction** with orlistat treatment in obese patients. METHODS AND RESULTS: Thirty-six obese (BMI: 36.1 +/- 3.4 kg/m2) and 11 non-obese (BMI: 22.9 +/- 1.7 kg/m2) subjects were studied. **IL-6** and hs-CRP levels were evaluated at baseline. In obese subjects after treatment of orlistat 120 mg three times daily for 6 months, **IL-6** and hs-CRP were repeated. Levels of circulating **IL-6** ($p < 0.05$) and hs-CRP ($p < 0.01$) were significantly higher in the obese group than in the non-obese group. Plasma **IL-6** ($r = 0.29$ and $p < 0.05$) and CRP ($r = 0.35$ and $p < 0.05$) concentrations correlated positively with the level of obesity assessed by BMI at baseline. After 6 months of orlistat treatment in obese subjects, the mean weight of the patients decreased by 6.8 kg, the BMI by 3.2 kg/m2. Compared with baseline, weight loss was associated with significant reductions of **IL-6** ($p < 0.001$) and hs-CRP ($p < 0.001$) levels. CONCLUSION: In summary plasma **IL-6** and hs-CRP levels were increased in obese patients. Orlistat-induced weight **reduction** was associated with decreasing levels of both **IL-6** and hs-CRP in obese subjects. Because inflammatory mediators may be directly involved in atherogenesis, this would suggest that interventions to **reduce IL-6** and CRP levels could be cardioprotective.

6/TI,AB/17
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Effects of bezafibrate on lipoprotein subclasses and **inflammatory markers** in patients with hypertriglyceridemia--a nuclear magnetic resonance study.
BACKGROUND: Hypertriglyceridemia is often associated with elevated remnants, small dense LDL and decreased HDL-cholesterol (C). The objective of this study was to investigate the efficacy of bezafibrate on lipoprotein subfractions profile and inflammation markers in patients with hypertriglyceridemia. METHODS: Twenty-four hypertriglyceridemic subjects took bezafibrate, 400 mg daily, for 4 weeks. Lipoprotein subclasses were measured by nuclear magnetic resonance (NMR) spectroscopy. Inflammation markers including C-**reactive protein** (CRP), interleukin-6 (**IL-6**) and monocyte chemotactic protein-1 (MCP-1) were also determined. RESULTS: Bezafibrate lowered triglyceride (TG) by 59% and increased HDL-C by 20%. NMR analysis revealed that bezafibrate lowered large TG-rich lipoproteins and IDL by 81% and 46%, respectively. Small LDL was selectively decreased by 53% with increase in large to intermediate LDL, thus altering the LDL distribution towards the larger particles (mean diameter 19.9 to 20.7 nm, $p = 0.0001$). Small (HDL1) and intermediate (HDL3) HDL significantly increased by 168% and 70%, whereby resulting in a significant **reduction** of the mean HDL particle size from 9.0 to 8.7 nm ($p = 0.026$). None of inflammation makers showed significant change by bezafibrate. CONCLUSIONS: Bezafibrate effectively ameliorates atherogenic dyslipidemia by reducing remnants and small LDL as well as by increasing HDL particles in hypertriglyceridemic subjects.

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Effect of preexisting statin use on expression of C-**reactive protein**, adhesion molecules, interleukin-6, and antioxidized low-density lipoprotein antibody in patients with unstable angina undergoing coronary stenting.

BACKGROUND: Statins are believed to **reduce** coronary heart disease by mechanisms in addition to their well-known cholesterol lowering effect. HYPOTHESIS: We studied the effect of statins on expression of **C-reactive protein** (CRP), interleukin-6 (**IL-6**), adhesion molecules, and antioxidized low-density lipoprotein antibody (anti-oxLDL Ab) in patients with unstable angina (Braunwald class IIb or IIIb) undergoing coronary stenting. METHODS: Consecutive 50 patients with unstable angina were included in the study. We classified the study subjects as patients using statins (Group A, n=20, men 10, mean age 62 years) and patients not using statins (Group B, n=30, men 15, mean age 60 years). RESULTS: Baseline levels of **inflammatory markers** were similar in the two groups. However, 24 h after coronary stenting, serum levels of CRP (2.00 vs. 4.63 mg/l, p < 0.05), intercellular adhesion molecule-1 (ICAM-1) (217 vs. 261 ng/ml, p < 0.01), and anti-oxLDL Ab (8.97 vs. 12.96 U/ml, p < 0.05) were significantly higher in Group B than in Group A. Furthermore, 72 h after coronary stenting, serum levels of CRP (3.00 vs. 5.50 mg/l, p < 0.01) and ICAM-1 (222 vs. 277 ng/ml, p < 0.05) were significantly higher in Group B than in Group A. CONCLUSIONS: Preexisting statin therapy plays a role in reducing the serum levels of CRP, ICAM-1, and anti-oxLDL Ab after coronary stenting in patients with unstable angina. These data support an anti-inflammatory or plaque-stabilizing effect of statin therapy.

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Glycoxidation and **inflammatory markers** in patients on treatment with PMMA-based protein-leaking dialyzers.
BACKGROUND: High-molecular-weight solutes such as glycation and oxidation protein products are putative proinflammatory mediators found in the uremic blood. The elimination of these and other large solutes by protein-leaking dialyzers (PLD) might help to correct the inflammatory status of maintenance hemodialysis (HD) patients. METHODS: Two matched groups of 13 standard 3 times/week HD patients were treated for 6 months with PMMA-based PLD and non-protein-leaking dialyzers (NPLD), respectively. At baseline, 1, 3, and 6 months, we measured the blood levels of the inflammatory cytokines IL-1beta, TNF-alpha, **IL-6**, the acute-phase protein **C-reactive protein** (CRP), the adhesion molecules ICAM-1, VCAM-1, and selectine-E, the chemptaxis factors MCP-1, and the glycation and oxidation protein end products pentosidine, protein carbonyls, and ACPP. RESULTS: In all the patients at baseline, pre-HD levels of glycation and oxidation protein markers, and inflammatory parameters were significantly higher than in healthy control subjects (P < 0.01 or greater). After 6 months, in the group on treatment with PLD, but not in that on NPLD, there was a significant decrease (P < 0.05 or greater) of pre-HD values of total pentosidine (mainly represented by pentosidine in serum albumin; -43%), protein carbonyls (-42%), ACPP (-38%), and the inflammatory cytokines IL-1beta (-49%), **IL-6** (-39%), and TNF-alpha (-20%), while IL-10 and INF-gamma increased by 67% and 37% respectively. Proinflammatory cytokines, and particularly **IL-6**, showed a positive correlation with the levels of circulating pentosidine. Protidemia was not significantly modified at the end of the study in both the groups. CONCLUSION: The results in this pilot study show that the removal of large solutes by PLD can improve some indices of chronic inflammation in HD patients. Further studies are required to determine the relevance of the individual solutes removed with PLD as proinflammatory mediators in the uremic environment.

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Weight reduction, but not a moderate intake of fish oil, lowers concentrations of **inflammatory markers** and PAI-1 antigen in obese men during the fasting and postprandial state.
BACKGROUND: In obese subjects, chronic low-grade inflammation contributes to an increased risk of metabolic abnormalities, which are reversed by weight loss. Substantial weight loss, however, is difficult to achieve and more insight into dietary approaches on anti-inflammatory responses in obese subjects is needed. In this respect, fish oil deserves attention. MATERIAL AND METHODS: Eleven obese men (BMI: 30-35 kg m(-2)) received daily fish oil (1.35 g n-3 fatty acids) or placebo capsules in random order for 6 weeks. Eight subjects continued with a weight **reduction** study that lasted 8 weeks. Mean weight loss was 9.4 kg. At the end of each experimental period a postprandial study was performed. RESULTS: Relative to fasting concentrations, interleukin-6 (IL-6) levels increased by 75% 2 h and by 118% 4 h after the meal (P < 0.001), when subjects consumed the control capsules. In contrast, **C-reactive protein** (C-RP) concentrations decreased slightly by 0.7% and 6.6% (P = 0.046), and those of plasminogen activator inhibitor-1 (PAI-1) antigen by, respectively, 26% and 53% (P < 0.001). Tumour necrosis factor-alpha (TNF-alpha; P = 0.330) and soluble TNF-receptor concentrations (sTNF-R55 and sTNF-R75; P = 0.451 and P = 0.108, respectively) did not change.

Changes relative to fasting concentrations were not significantly affected by either fish oil or weight **reduction**. Absolute IL-6, C-RP, sTNF-R55, sTNF-R75, and PAI-1 antigen concentrations, however, were consistently lower after weight **reduction**, but not after fish oil consumption. CCNCLUSICN: For slightly obese subjects a moderate intake of fish oil does not have the same favourable effects on markers for a low-grade inflammatory state as weight **reduction**.

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Effect of liposuction on insulin resistance and vascular **inflammatory markers** in obese women.

Liposuction is one of the more common elective surgical procedures in the US and is supposed to be on the increase. There are no reported studies specifically addressing the metabolic sequelae of liposuction in obesity. The aim of the present study was to investigate the role of large-volume liposuction on insulin resistance and circulating **inflammatory markers** in obese people. Thirty healthy premenopausal obese (body mass index (BMI) from 30 to 45) and 30 age-matched normal weight (BMI <25) women were studied. In obese women, insulin sensitivity, as measured by the Homeostasis Model Assessment (HOMA=fasting plasma glucose x fasting serum insulin divided by 25), as well as serum adiponectin, the novel adipocytokine with insulin sensitising properties, were significantly lower, as compared with nonobese women (p<0.01), indicating insulin resistance; on the contrary, serum concentrations of the proinflammatory cytokines IL-6, IL-18 and TNF-alpha, as well as the sensitive marker of inflammation **C-reactive protein**, were significantly higher (p<0.01). All obese women were submitted to a single large volume liposuction (superwet technique): the mean aspirate volume was 3540 ml (range 2550-4670), corresponding to a net lipid loss of 2.7+/-0.7 kg (mean+/-SD). After six months of stable body weight after liposuction, women were less insulin resistant (p<0.05), had reduced concentrations of **IL-6**, IL-18, TNF-alpha and CRP (p<0.05-0.02), and increased serum levels of adiponectin (p<0.02) and HDL-cholesterol (p<0.05). There was a significant correlation between the amount of fat aspirate and changes in HOMA (r=0.28, p<0.05), TNF-alpha (r=0.31, p<0.02), and adiponectin (r=-0.34, p<0.02), as well as between the decrease in TNF-alpha and the increase in adiponectin after the surgical procedure (r=-0.45, p<0.01). Our study demonstrates that liposuction is safe and free of metabolic sequelae in obese women, pending a careful screening of the patient. Moreover, it is associated with amelioration of insulin resistance and reduced circulating markers of vascular inflammation which may help obese subjects to **reduce** their cardiovascular risk.

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Periodontitis and systemic inflammation: control of the local infection is associated with a **reduction** in serum **inflammatory markers**.

Severe periodontitis is associated with elevated **inflammatory markers** in otherwise healthy populations. However, the nature of this association has not been determined. Our aim was to assess whether the degree of response to periodontal therapy was associated with changes in serological markers of systemic inflammation. Ninety-four systemically healthy subjects with severe generalized periodontitis participated in a prospective six-month blind intervention trial. Periodontal parameters and **inflammatory markers** [**C-reactive Protein** (CRP) and Interleukin-6 (**IL-6**)] were evaluated prior to and 2 and 6 mos after delivery of standard non-surgical periodontal therapy. Six months after treatment, significant reductions in serum **IL-6** (p < 0.001, median decrease 0.2 ng/L, 95% CI 0.1-0.4 ng/L) and CRP (p < 0.0001, median decrease 0.5 mg/L, 95% CI 0.4-0.7) were observed. Decreases in **inflammatory markers** were significant in subjects with above average clinical response to periodontal therapy after correction for possible confounders. Periodontitis may add to the systemic inflammatory burden of affected individuals.

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Effect of eicosapentaenoic acid and docosahexaenoic acid on oxidative stress and **inflammatory markers** in treated-hypertensive type 2 diabetic subjects.

n-3 fatty acids **reduce** the risk of cardiovascular disease via a number of possible mechanisms. Despite this, there has been concern that these fatty acids may increase lipid peroxidation. The data in vivo are inconclusive, due in part to limitations in the methodologies. In this regard, the measurement of F2-isoprostanes provides a reliable assessment of in vivo lipid peroxidation and oxidant stress. This study aimed to

assess the effects of supplementation with purified eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), the two major n-3 fatty acids, on urinary F2-isoprostanes and markers of inflammation, in type 2 diabetic patients. In a double-blind, placebo controlled trial of parallel design, 59 nonsmoking, treated-hypertensive, type 2 diabetic subjects, were randomized to 4 g daily of purified EPA, DHA, or olive oil for 6 weeks, while maintaining their usual diet. F2-isoprostanes, measured using gas chromatography-mass spectrometry in 24 h urines and C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), were measured before and after intervention. Thirty-nine men aged 12 women aged 61.2 +/- 1.2 years, with body mass index (BMI), 29.5 +/- 0.5 kg/m2; 24 h blood pressure, 138/73 mmHg; HbA1c, 7.3 +/- 0.1% and fasting glucose, 7.9 +/- 0.2 mmol/l completed the intervention. Baseline urinary F2-isoprostanes were positively associated with HbA1c (p=.011) and fasting glucose (p=.032). Relative to the olive oil group, post-intervention urinary F2-isoprostanes were decreased 19% by EPA (p=.017) and 20% by DHA (p=.014). There were no significant changes in CRP, IL-6, and TNF-alpha following EPA or DHA supplementation. In regression analysis, Delta F2-isoprostanes were positively associated with Delta HbA1c (p=.007) independent of treatment group; and with Delta TNF-alpha (p=.034) independent of age, gender, BMI, and treatment group. There were no associations with Delta CRP or Delta IL-6. This study is the first report demonstrating that either EPA or DHA reduce in vivo oxidant stress without changing markers of inflammation, in treated hypertensive, type 2 diabetic subjects.

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High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study.
BACKGROUND: Inflammation promotes acute coronary syndromes and ensuing clinical complications. Although statins reduce inflammatory markers in asymptomatic adults or in patients with stable angina, the effect of statins on the markedly heightened inflammation in patients with acute coronary syndromes is unknown. METHODS AND RESULTS: We measured C-reactive protein (CRP), serum amyloid A (SAA), and interleukin 6 (IL-6) in 2402 subjects enrolled the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study. Subjects with unstable angina or non-Q-wave myocardial infarction were randomized to atorvastatin 80 mg/d or placebo within 24 to 96 hours of hospital admission and treated for 16 weeks. The effect of treatment on inflammatory markers was assessed by ANCOVA after adjustment for presenting syndrome, country, and initial level of marker. All 3 markers were markedly elevated at randomization and declined over the 16 weeks in both treatment groups. Compared with placebo, atorvastatin significantly reduced CRP, -83% (95% CI, -84% -81%) versus -74% (95% CI, -75% -71%) (P<0.0001) and SAA, -80% (95% CI, -82% -78%) versus -77% (-79% -75%) (P=0.0006) but not IL-6, -55% (95% CI, -57% -53%) versus -53% (95% CI, -55% -51%) (P=0.3). Reductions in CRP and SAA were observed in patients with unstable angina and non-Q-wave myocardial infarction, with initial LDL cholesterol <3.2 or > or =3.2 mmol/L (125 mg/dL), age > or =65 or <65 years, and in men and women. By 16 weeks, CRP was 34% lower with atorvastatin than with placebo. CONCLUSIONS: High-dose atorvastatin potentiated the decline in inflammation in patients with acute coronary syndromes. This supports the value of early statin therapy in these patients.

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Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial.
CONTEXT: Obesity is an independent risk factor for cardiovascular disease, which may be mediated by increased secretion of proinflammatory cytokines by adipose tissue. OBJECTIVE: To determine the effect of a program of changes in lifestyle designed to obtain a sustained reduction of body weight on markers of systemic vascular inflammation and insulin resistance. DESIGN AND SETTING: Randomized single-blind trial conducted from February 1999 to February 2002 at a university hospital in Italy. PATIENTS: One hundred twenty premenopausal obese women (body mass index > or =30) aged 20 to 46 years without diabetes, hypertension, or hyperlipidemia. INTERVENTIONS: The 60 women randomly assigned to the intervention group received detailed advice about how to achieve a reduction of weight of 10% or more through a low-energy Mediterranean-style diet and increased physical activity. The control group (n = 60) was given general information about healthy food choices and exercise. MAIN OUTCOME MEASURES: Lipid and glucose intake; blood pressure; homeostatic model assessment of insulin sensitivity; and circulating levels of interleukin 6 (IL-6), interleukin 18 (IL-18), C-reactive protein (CRP), and adiponectin. RESULTS: After 2

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years, women in the intervention group consumed more foods rich in complex carbohydrates (9% corrected difference; P<.001), monounsaturated fat (2% P =.009), and fiber (7 g/d; P<.001); had a lower ratio of omega-6 to omega-3 fatty acids (-5; P<.001); and had lower energy (-310 kcal/d; P<.001), saturated fat (-3.5% P =.007), and cholesterol intake (-92 mg/d; P<.001) than controls. Body mass index decreased more in the intervention group than in controls (-4.2; P<.001), as did serum concentrations of IL-6 (-1.1 pg/mL; P =.009), IL-18 (-57 pg/mL; P =.02), and CRP (-1.6 mg/L; P =.008), while adiponectin levels increased significantly (2.2 microg/mL; P =.01). In multivariate analyses, changes in free fatty acids (P =.008), IL-6 (P =.02), and adiponectin (P =.007) levels were independently associated with changes in insulin sensitivity. CONCLUSION: In this study, a multidisciplinary program aimed to reduce body weight in obese women through lifestyle changes was associated with a reduction in markers of vascular inflammation and insulin resistance.

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